

# Systematic Literature Review of Basal Bolus Insulin Analogue Therapy during Pregnancy

**Research Article**

Volume 3 Issue 2 - 2015

**Shadi Rezaei<sup>1</sup>, Sara Yuen<sup>2</sup>, Jason Lam<sup>2</sup>, Andrei Hastings<sup>2</sup>, Ray Mercado<sup>1</sup> and Cassandra E Henderson<sup>1</sup>**<sup>1</sup>Department of Obstetrics and Gynecology, Lincoln Medical and Mental Health Center, USA<sup>2</sup>St. George's University, School of Medicine, West Indies**\*Corresponding author:** Cassandra E Henderson, CDE, Director of Maternal Fetal Medicine, Lincoln Medical and Mental Health Center, 234 East 149th Street, Bronx, NY, 10451; USA, Email: Cassandra.henderson@nychhc.org**Received:** October 17, 2015 | **Published:** November 23, 2015**Abstract**

Currently standard insulin therapy for pregnancies complicated by diabetes mellitus (DM) is a combination of intermediate Neutral Protamine Hagedorn (NPH) and regular human insulin. In contrast, for non-pregnant individuals with diabetes, standard insulin therapy is basal bolus therapy (BBT) using a combination of rapid- and long-acting insulin analogues designed to mimic physiologic biphasic insulin secretion by the pancreatic beta cells. Although there are published reports describing use of BBT during pregnancy, due to the lack of strong clinical evidence regarding safety and efficacy of BBT during pregnancy, its use has not been adopted as standard insulin administration during pregnancies complicated by diabetes mellitus. To evaluate the evidence for this discrepant clinical management, we conducted a systematic review. Search strategy and selection criteria: PubMed, Medline, Cochrane Database of Systematic Reviews for publications between 1996 and 2014. Search terms: lispro, aspart, glargine, detemir, glulisine, Humalog, NovoLog, Lantus, Levemir, Apidra, pregnancy, and diabetes. Included: randomized clinical trials, prospective and retrospective cohort analyses, case-control studies and case series and reports. Search limited to human studies and English language. Excluded: review articles. Nineteen studies were identified that assessed safety/efficacy of rapid-acting insulin analogues, lispro and aspart, and 23 studies that assessed the long-acting insulin analogues, glargine and detemir, in pregnant patients complicated with pregestational (PGDM) and gestational diabetes mellitus (GDM). The principal efficacy endpoint examined in the selected studies was glycated hemoglobin levels. Other study outcome variables to assess maternal glycemic control included fasting and postprandial glucose levels, large for gestational age (LGA) infants, mean birth weight, congenital malformations, and incidence of hypoglycemic events. Compared to conventional insulin therapy, insulin analogue use provided similar overall glycemic control in pregnancy. In addition, they contributed to greater postprandial glucose control. There was no compelling evidence that insulin analogue use was associated with any significant differences in maternal and neonatal outcomes, particularly in terms of incidences in maternal and neonatal hypoglycemia, LGA, and congenital malformations. Given the documented benefits of physiological insulin replacement, we found no reason that BBT should not be standard prenatal care for pregnancies complicated by DM.

**Keywords:** Apidra; Aspart; Detemir; Diabetes; DM; Glargine; Glulisine; Humalog; Insulin Analogues; Insulin Type; Insulin; Intermediate-Acting; Lantus; Levemir; Lispro; Literature Review; Long Acting Insulin Analogues; Long-Acting; NovoLog; NPH; Pregnancy; Rapid-Acting; Short Acting Insulin Analogues

**Introduction**

The maternal, fetal and neonatal complications of having diabetes during pregnancy, whether pre-gestational (PGDM) or gestational (GDM), have been well-established in the literature, prompting recommendations that women achieve and maintain strict glycemic control before and during pregnancy [1]. DM-associated maternal complications include progression of retinopathy, nephropathy, hypertension, and preeclampsia. DM-associated fetal and neonatal complications include congenital malformations, stillbirth, macrosomia, shoulder dystocia, intrauterine growth restriction (IUGR) [2,3]. Poor glycemic control (glycated hemoglobin (A1c)  $\geq 7\%$ ) in the first trimester (T1) is associated with an increased rate of major congenital malformations and spontaneous abortions. In the third trimester (T3), poor glycemic control is associated with increased rate of preterm birth, preeclampsia and perinatal mortality [2,4].

However, simply targeting A1c levels is inadequate to prevent such complications. Insulin requirements vary throughout pregnancy: increasing in early pregnancy (for mean requirement of 0.7 units/kg), may decrease in the second half of T1, likely due to nausea and vomiting, then increase in second trimester (T2) (mean 0.8 units/kg) and T3 (mean 0.9-1.0 units/kg), and lastly, either plateaus or decreases beyond 32 weeks' gestation [5]. Insulin dosing must be continually managed and altered on an individual basis. Therefore, stringent glycemic control during pregnancy strives to minimize glucose excursions throughout the day [6].

Physiologic pancreatic beta cell secretion of insulin consists of a continuous rate of basal insulin and stimulated bolus insulin, released in response to an exogenous glucose load. Basal insulin secretion regulates lipolysis and hepatic glucose production in between meals [7]. Conventional insulin therapy during pregnancy includes human regular insulin and neutral protamine Hagedorn

(NPH); these fail to optimally simulate physiologic insulin release [8]. Through the advent of recombinant DNA techniques, both rapid- and long-acting analogues were used to create products that mimic physiologic insulin profiles [6]. Without the use of continuous subcutaneous insulin infusion, basal-bolus therapy (BBT), most closely simulates physiologic insulin profiles with the use of a long-acting insulin analogue used as basal insulin, coupled with a rapid-acting analogue given preprandially [1]. It is known that GDM increases a woman's risk of developing future type 2 diabetes mellitus (T2DM) [9]. Having patients become familiar with BBT during pregnancy could improve continuity of care for women with PGDM and those with GDM, who may later develop T2DM.

The conventional regular insulin has a 30-minute onset of action (Table 1). This delayed onset of action requires it be administered 30 minutes prior to meals [8]. In clinical practice, however, rapid-acting analogues get substituted for regular insulin in the conventional insulin regimen. Patients administer regular insulin immediately prior to meals and consequently, patients experience postprandial hyperglycemia, followed by hypoglycemia 30 minutes later [1]. Rapid-acting insulin analogues, like insulin aspart, lispro and glulisine are better options for simulating physiologic postprandial insulin action, allowing for more convenient dosing- immediately preprandially. Compared to regular insulin, rapid-acting insulin is associated with lower rates of 1- and 2-hour postprandial hyperglycemia. This may be important for perinatal outcome as postprandial hyperglycemia is more predictive of neonatal complications than is elevated fasting blood glucose levels [6,7]. Rapid-acting analogues also reduce the risk of late postprandial hypoglycemia, helping to minimize daily glucose excursions [10].

NPH is an intermediate-acting insulin used as a basal insulin that fails to mimic physiologic insulin secretion. It has a delayed onset of 2-4 hours, peaking in 4-10 hours, and lasting 12-18 hours (Table 1), whereas glargine and detemir successfully create a near peakless action profile [7,8]. Glargine has a duration of action of approximately 24 hours, whereas detemir has a shorter duration of action of 20 hours (Table 1). Clinically, this requires the use of multiple daily doses of NPH that rarely achieve a steady state of basal insulin. Whereas steady state basal insulin is achieved with the use of long-acting insulin analogues. Daily doses of basal insulin detemir requires twice daily dosing, while glargine necessitates once daily dosing [8]. Benefits of long-acting analogues include lower serum fasting glucose levels, reduced risk of nocturnal hypoglycemia and, less glycemic variability [10].

BBT using insulin analogues is standard care for non-pregnant individuals affected by T2DM. However, due to the lack of adequately powered randomized clinical trials evaluating the antenatal use of BBT, its routine use during pregnancy is not recommended by most experts. A review of the literature suggests that when compared to the current standard therapy (NPH and regular insulin regimen), BBT with insulin analogues used as therapy for pregnancies complicated by PGDM and GDM during pregnancy, have been associated with improved patient satisfaction and glycemic control [8,11]. We suggest these reported benefits as well as enabling therapeutic continuity for gravidas with PGDM, that insulin analogues become standard of insulin care during pregnancy. The widespread, often inadvertent

use of BBT during pregnancy, will likely prevent conduction of an adequately powered randomized trial to compare the perinatal risks and benefits of BBT versus standard perinatal insulin regimen, therefore we conducted a systematic literature review of insulin analogue use during pregnancy to evaluate the evidence concerning BBT use in pregnancy.

## Methods

Electronic literature search using PubMed, Medline, Cochrane Library were performed for randomized clinical trials, prospective, retrospective, observational, case reports and case series, using search terms, insulin analogues, lispro, aspart, detemir, glargine, glulisine, Humalog, NovoLog, Lantus, Levemir, Apidra, pregnancy, and diabetes, that were published between 1996 and 2014. Studies included case reports and series, randomized clinical trials, prospective and retrospective observational studies evaluating rapid and long-acting insulin analogues in pregnancies complicated by either PGDM or GDM. Studies assessing efficacy, safety, and historical comparisons between analogues were included. Review articles were excluded. Search was limited to human studies and in the English language. The principal efficacy endpoint examined was glycemic control through A1c levels. Maternal safety outcomes were incidence of hypoglycemic events, fasting and postprandial hyperglycemia. Neonatal outcomes included rate of large for gestational age (LGA) or macrosomic (>4000g birth weight) infants, mean birth weight, rate of congenital malformations, and incidence of hypoglycemic events.

## Results

Nineteen reports were identified that assessed the use of rapid-acting insulin analogues, lispro and aspart, as hypoglycemic agents during pregnancy. Their prenatal use was associated with significant decreases in A1c, incidence of maternal hypoglycemia, comparable rates of neonatal hypoglycemia and congenital malformations when compared to regular insulin use. Twenty-three reports assessed the safety and efficacy of the long-acting insulin analogues, glargine and detemir. These agents were associated with significant decreases in A1c, maternal and neonatal hypoglycemia with no increase in rates of LGA/macrosomia infants or congenital malformations.

A total of 42 studies were included. Of those, 3 were uncontrolled studies of lispro, 10 were either observational or randomized studies comparing insulin lispro to NPH insulin. Mecacci et al. [12] compared lispro and regular insulin to healthy controls, rather than to each other. Three publications on randomized controlled trials comparing insulin aspart to NPH insulin were included; of these, Mathiesen et al. [13] and Hod et al. [14] reported on the same study. One study compared both rapid-acting insulin analogues (lispro and aspart) to regular insulin. Four uncontrolled observational studies of glargine were included, 7 studies compared glargine use to NPH and one study compared glargine to detemir. Of the 7 studies comparing glargine to NPH, Imbergamo et al. [15] compared glargine users to healthy controls for fetal and neonatal outcomes. Two uncontrolled studies of detemir were included and 2 publications by Mathiesen et al. [13] and Hod et al. [14] reporting on the same randomized controlled trial comparing detemir to NPH were included.

## Rapid-Acting Insulin analogues

**Glulisine:** There are no published reports of the use of insulin glulisine in pregnancy.

**Lispro:** Lispro is the most well-studied insulin analogue used during pregnancy. An early case report by Diamond & Kormas [16] reported possible adverse fetal effects of lispro in 2 diabetic mothers. One pregnancy was terminated and was found to have multiple heart abnormalities, polysplenia, and abdominal situs inversus. The second infant was born at full term and died suddenly at 3 weeks' and was found to have congenital diaphragmatic hernia and bilateral undescended testes [16].

Three uncontrolled studies evaluated the effects of lispro during pregnancies complicated by PGDM (Tables 2a & 2b). Masson et al. [17] included data from 71 subjects with T1DM and reported decreased A1c from levels in the preconception period to T3 (7.4±1.7 to 6.17±0.85). Early during gestation, the authors reported that 12 women experienced 12 episodes of severe hypoglycemia. In terms of neonatal outcomes, 2 had congenital malformations, 29 neonates had hypoglycemia, and 35% had birth weights of ≥90th percentile for gestational age [17]. Garg et al. [18] studied 62 parturients with T1DM treated with lispro, who had a mean preconception A1c of 7.2±0.2, that decreased to 5.8±0.1 at delivery. Fourteen gravida experienced severe hypoglycemic episodes or 0.61 events/patient. Two neonates had congenital malformations and 24% were LGA [18]. A retrospective cohort analysis from Wyatt et al. [19] of 496 women with PGDM treated with lispro found a mean A1c value at the first prenatal visit of 8.9±4.2 to be significantly reduced to 6.2±2.4 in T3 (p<0.001). The rates of major congenital abnormalities, LGA infants, and mean birth weight were 5.4% (95% CI [3.45-7.44%]) and 23.4%, and 3464±765g, respectively [19].

Twelve studies (4 randomized trials and 8 observational studies) comparing both maternal and neonatal outcomes in PGDM and GDM treated with lispro versus human insulin are reported in Tables 2a & 2b. Jovanovic et al. [20] randomized 42 women diagnosed with GDM between 14 and 32 weeks' of gestation, who were insulin naïve, to lispro (19 women) and regular insulin (23 women). A test meal consisting of 20% of daily caloric need was given before breakfast and followed by subcutaneous injection of the calculated initial daily insulin of either lispro or regular insulin. Scheduled measurement of glucose concentrations were fasting, 60 min, 120 min, and 180 min following the meal. The authors reported significantly lesser area under the curve for lispro (p=0.025). However, A1c measured 6 weeks later showed no significant differences between groups (p=0.7508). The group treated with lispro experienced fewer pre-breakfast hypoglycemic events (<55 mg/dL), but not before lunch or dinner. Mean birth weight, frequency of macrosomia, intrauterine growth restriction (IUGR), and fetal abnormalities did not significantly differ [20].

Buchbinder et al. [21] retrospectively analyzed patients with T1DM treated with lispro (n=12) and regular insulin (n=42). Overall, there were no statistically significant differences in glycemic control between the 2 groups during pregnancy and postpartum [21]. Similarly, Bhattacharyya et al. [22] conducted a retrospective cohort study of PGDM and GDM patients and demonstrated no differences in fetal outcomes. However, pre-

delivery A1c levels in the lispro group were significantly lower than regular insulin and diet-controlled groups (p<0.05). In addition, patient satisfaction was significantly higher in the lispro group compared to regular insulin (26.3±2.3 vs. 18±8.9, p=0.0005) [22].

Loukovaara et al. [23] conducted a randomized trial on women with T1DM (lispro, n=36 and regular insulin, n=33). They found lower, but non-significant, rates of maternal hypoglycemia (9 vs. 11 women, p=0.42) throughout pregnancy. A1c levels were significantly lower in the lispro group in T2 and T3, but not in T1 (p=0.022) [23].

No significant difference was demonstrated in A1c levels in any trimester in a prospective observational and retrospective observational study by Cypryk et al. & Aydin et al. respectively [24,25]. By contrast, Lapolla et al. [26] reported a significantly lower A1c level in T1 in the lispro versus regular group (6.7±1.4 vs. 7.3±1.4, p<0.001), but no difference in A1c in T3 (6.0±1.0 lispro vs. 6.2±1.2 regular) [26]. Rates of maternal hypoglycemia were lower but non-significant in the lispro group (2.8% vs. 5.4%). Incidences of congenital malformations were similar (4.3% vs. 4.5%). However, incidence of LGA was significantly higher in the lispro group (55.1% vs. 39.2%, p=0.0267). Cypryk et al. [24] demonstrated a non-significant decrease in the rate of neonatal hypoglycemia (17.4% in lispro group vs. 23.3% in regular insulin group). There were no reports of congenital malformations in either study.

In 2002, randomized controlled trial conducted by Persson et al. [27] randomized 16 women to lispro and 17 to regular insulin at 14 weeks' gestational age. Postprandial breakfast glycemic control significantly improved in the lispro compared to regular insulin group (p<0.01). Only one congenital malformation with regular insulin was reported. Although there was an associated increase in rate of maternal biochemical hypoglycemic events (<54 mg/dL) in those treated with insulin lispro (5.5 vs. 3.9%, p<0.05), only the regular insulin group experienced severe hypoglycemia episodes [27].

Mecacci et al. [12] enrolled 25 patients on lispro and 24 on regular insulin in a randomized trial of women with GDM, and compared them to 50 healthy controls. The 1-hour postprandial blood glucose concentrations were significantly higher in the regular insulin group, but similar for the 2 study groups at 2-hours. The rate of neonates born with a cranio-thoracic circumference ratio between the 10th and 25th percentile was significantly higher in the regular insulin group. The authors found no differences in neonatal outcomes between treatment groups [12].

In 2005, Plank et al. [28] found no significant differences in fetal or maternal outcome between pregnant patients using insulin lispro and aspart [28]. A prospective observational study by Durwald et al. [29] demonstrated significantly improved A1c over T2 and T3 in those treated with insulin lispro versus regular insulin (5.9±1.0 vs 6.7±1.3, p=0.009). In addition, while the mean birth weight was significantly higher in the lispro group (3569±526g vs. 3246±764g, p=0.01), the incidence of LGA (32.8% vs. 20.4%, p=0.15) and neonatal hypoglycemia (41.4% vs. 38.8%) in the study groups were not statistically significant. Congenital

malformation was identified in one patient exposed to lispro and two in the regular insulin group [29].

In 2011, Garcia-Dominique et al. [30] retrospectively evaluated 241 parturients treated with regular insulin and NPH and 110 with various combinations of insulin analogues (most commonly, a combination of lispro and NPH) [30]. The group treated with insulin analogues had slightly higher mean A1c during T1 ( $6.9 \pm 1.0$  vs.  $6.6 \pm 1.0$ ,  $p=0.022$ ), but required smaller insulin doses throughout pregnancy. The frequency of severe hypoglycemia was significantly less among rapid-acting analogue users (2.3 vs. 10.0%,  $p=0.025$ ). The treatment groups had similar rates of congenital malformations. In contrast, neonatal hypoglycemia was significantly more frequent in the rapid-acting analogue group (34.9 vs. 23.6%,  $p=0.043$ ), but the authors attributed this to the concomitant use of an insulin pump.

Di Cianni et al. [31] conducted a smaller clinical trial of women with GDM who were randomized to receive lispro, aspart or regular insulin with NPH as basal insulin [31]. The groups were matched for age, parity, BMI, gestational age and weight gain. One-hour postprandial glucose levels after breakfast were significantly higher in the regular insulin group when compared to the lispro and aspart groups ( $135 \pm 23.4$ ,  $118.8 \pm 18.9$ ,  $121.5 \pm 20.16$  mg/dL, respectively, ANOVA  $p < 0.05$ ). Birth weight was higher in the regular insulin group ( $p < 0.04$ ) and similarly, LGA rates were 15.6%, 12.1%, and 9.6% in regular insulin, lispro, and aspart groups, respectively.

To date, there are two published papers who performed a meta-analysis comparing lispro to regular insulin. One article by Gonzalez Blanco et al. [32] looking at only T1DM, included four studies into their analysis revealed no differences in maternal or neonatal outcomes with the exception of a higher rate of LGA newborns (RR 1.38 [1.14-1.68]) [32]. A larger and more recent meta-analysis by Lv et al. [33] assessed the safety of four insulin analogs: lispro, aspart, glargine, and detemir. Twenty-four studies met their inclusion criteria which involved both pre-gestational and gestational diabetic pregnant patients. They reported no significant difference in the maternal and neonatal outcomes in patients using aspart, glargine, and detemir. However, insulin lispro was associated with higher birth weight and an increased rate of LGA newborns, similar to the findings of the previous meta-analysis [33].

**Aspart:** Aspart use in pregnancy has not been as well studied as has been with lispro. We have included four studies that evaluate the use of aspart in pregnancy (Tables 3a & 3b).

The first published study was authored by Pettitt et al. [34] in 2003 (Table 3). Twenty-seven women with GDM were enrolled in a prospective cross-over trial. Area under the curve of glucose concentrations from the preprandial period to 240 minutes after a test meal consisting of 20% of daily caloric needs were measured. Either aspart or regular insulin was given the first day, which was followed by administration of the other insulin the next day. The area under the curve was significantly lower with aspart ( $p=0.018$ ) but not with regular insulin ( $p=0.997$ ), compared to no insulin use. One congenital malformation was reported in the aspart group. The authors reported no macrosomic infant in either group [34].

A large open-label, randomized, parallel-group trial by Mathiesen et al. [13] and Hod et al. [14] investigated 322 women

with T1DM, who had been treated with insulin for more than 12 months and had preconception A1C  $< 8\%$  [13,14]. Subjects were randomized to aspart or regular insulin, coupled with NPH used as basal insulin. The primary study endpoint was major maternal hypoglycemia (requiring assistance with  $< 55.8$  mg/dL or reversal of symptoms after food, glucagon, or intravenous glucose); this was not significantly lower in the group treated with aspart (RR 0.720 [95% CI 0.36-1.46]). Both groups showed decreased A1c during T1 and T2, followed by an increase at delivery and at 6 weeks' postpartum. No statistical significance in glycemic control was reported in T2 and T3. The incidence of congenital malformations was 4.3% and 6.6% for aspart and regular insulin, respectively. There were no significant differences between treatment arms in birth weight and rates of neonatal hypoglycemia requiring treatment (33.6% aspart vs. 39.7% regular insulin). In addition, the aspart treatment group had greater overall treatment satisfaction due to increased flexibility in treatment and is demonstrated by their willingness to continue on the study regimen after delivery.

Heller et al. [35] published a randomized, multicenter trial of 322 women affected by T1DM in 2010; 99 of these patients were randomized pre-pregnancy and 223 randomized early during the pregnancy, to either aspart or regular insulin for bolus therapy, in combination with NPH for basal therapy. They found no differences in A1c levels between treatment groups, but also demonstrated fewer, but not statistically significant, maternal hypoglycemic episodes with aspart use versus regular insulin (0.9 vs. 2.4 events per patient per year in the first half of pregnancy, and 0.3 vs. 1.2 events per patient per year in the second half of pregnancy) [35].

See above Lispro section for results from Di Cianni et al. [31].

### Long Acting Insulin Analogues

**Glargine:** To date, there are no randomized trials studying the safety and efficacy of glargine use during pregnancy. However, glargine is the long-acting insulin analogue that has been well studied through case reports and observational studies (Tables 4a & 4b).

The first reports of glargine use in pregnancy stem from a set of case reports published between 2002 and 2007. Few pregnant patients were switched from NPH to glargine due to recurrent hypoglycemic episodes. Others had either willingly continued using glargine despite the unknown effects or was not aware of their pregnancy until 6-12 weeks' gestation. No congenital malformations were reported, although two infants were LGA [36-42].

In 2008, Gallen et al. [43] published an uncontrolled prospective audit of 115 pregnant women with T1DM treated with glargine. Of these, 69% were treated with glargine during the preconception period. Lispro was the bolus insulin in 42%, aspart in 45%, and regular insulin in 8%. Glycemic control assessed by changes in A1c levels improved from enrollment ( $8.1 \pm 1.7$ ) to T3 ( $6.8 \pm 0.1$ ). Severe maternal hypoglycemia, defined as requiring third-party assistance, was reported in 22%. In terms of neonatal outcomes, 47% (50/114) of neonates experienced hypoglycemia, mean birth weight was  $3500 \pm 600$ g, and three had congenital abnormalities [43].

Similarly, Lepercq et al. [44] studied 102 women with T1DM

treated with glargine and demonstrated improvement in mean A1C from T1 to T3 ( $6.7 \pm 1.2$  to  $6.2 \pm 0.9$ ). Two congenital malformations were noted and LGA rate was 30% [44]. Henderson et al. [45] conducted a retrospective review of 240 women with T2DM and GDM and found a mean glucose level of  $112 \pm 14.8$  mg/dL, birth weight of  $3142 \pm 606$ g and 4 macrosomic infants [45].

Di Cianni et al. [46] retrospectively observed a cohort of 107 women who used glargine for at least one month preconception and during pregnancy. Six pregnancies ended with abortion, 4 of which were spontaneous. The comparison groups were 43 women who had continued with glargine throughout pregnancy and 58 women who started using glargine in early pregnancy and switched to NPH, based on individual center policies. All patients showed improvement in glycemic control during pregnancy measured as A1c, from  $7.7 \pm 1.32$  at first prenatal visit to  $6.5 \pm 0.79$  at end of pregnancy in glargine group and  $7.6 \pm 1.09$  to  $6.5 \pm 0.91$  in NPH group. Maternal hypoglycemia was reported in 9.3% and 12.1% in glargine and NPH groups, respectively. The rates of LGA, macrosomia, congenital malformations and neonatal hypoglycemia were comparable between groups [46].

Price et al. [47] conducted a case-control study in women with T1DM and GDM. Thirty-two women previously treated with glargine were selected (10 T1DM, 22 GDM) using either lispro or aspart for bolus therapy. Cases were matched for type and duration of diabetes, duration of insulin therapy during pregnancy, parity, maternal height, and weight at first prenatal visit, gestational age at delivery, fetal sex, and glycemic control. Third trimester glycemic control and incidence of daytime and nocturnal hypoglycemia were not significantly different between groups. Birth weight and rate of congenital abnormalities were similar. Overall incidence of macrosomia was similar: 37.5% in glargine group and 40.6% in control group ( $p > 0.05$ ) [47].

Poyhonen-Alho et al. [48] conducted a case-control study of women with T1DM. Forty-two received glargine, while 49 were treated with NPH. The glargine group demonstrated a significantly greater decrease in A1c from T1 to T3 ( $0.8 \pm 0.1$ ) versus NPH ( $0.3 \pm 0.2$ ) ( $p = 0.04$ ). Maternal hypoglycemia rates and birth weight did not differ [48]. Similarly, rates of mild and severe hypoglycemia did not differ either between glargine and NPH in a smaller study from Imbergamo et al. [15]. Glargine group had significantly improved fasting and 2-hour post-breakfast glucose levels during T1 and T2. However, the incidence of LGA was 46.7% and 27.6% in the glargine and NPH groups, respectively. No differences in maternal or neonatal outcomes were found in a retrospective analysis by Smith et al. [49].

Fang et al. [50] studied 112 PGDM and GDM women; they compared glargine and NPH use in 2 different patient populations: PGDM and GDM patients. Regular insulin or lispro was used as the prandial insulin regimen. They found no significant differences in the rates of maternal hypoglycemia, T3 A1c levels, and mean birth weight. No congenital abnormalities were noted. In PGDM treated with glargine, 18.9% had LGA infants versus 50% in NPH group (RR 0.38, 95% CI [0.17–0.87],  $p = 0.04$ ). There was only one case of maternal hypoglycemia in the PGDM group treated with glargine. There were no cases of neonatal hypoglycemia in PGDM glargine group, while 25% of the neonates exposed to in utero to NPH ( $p = 0.01$ ) experienced neonatal hypoglycemia. Subgroup analysis

found no differences in rates of LGA or of neonatal hypoglycemia in GDM groups between insulin glargine and NPH use [50].

Egerman et al. [51] evaluated outcomes for 114 women with PGDM and GDM women treated with NPH and insulin glargine. The only significant differences in maternal and neonatal outcomes was an increased incidence of shoulder dystocia in the NPH group ( $p = 0.03$ ) [51]. A recent study published in 2010, was a prospective cohort study of 138 women with either PGDM or GDM; PGDM and GDM groups were analyzed separately. Maternal hypoglycemia rates were increased in NPH versus glargine. The PGDM group treated with glargine experienced no hypoglycemic episodes, while 23% of the NPH group experienced hypoglycemia ( $p < 0.0001$ ). The neonatal outcomes for the study groups were not different [52].

Callesen et al. [53] retrospectively observed 113 women with T1DM and compared 2 basal insulin analogues, glargine and detemir. Median A1c levels at 8 weeks' and 33 weeks' for the 2 study groups were comparable. In both groups, 23% experienced at least one occurrence of severe hypoglycemia. Lower mean birth weight ( $p = 0.05$ ) and incidence of LGA infants ( $p = 0.046$ ) were demonstrated in the glargine group [53].

One meta-analysis of maternal and neonatal outcomes comparing the use of glargine vs NPH insulin incorporating eight studies was conducted by Lepercq et al. [54] in 2012. They reported no significant increased risk of any neonatal or maternal outcomes. They also found no difference in the glycemic control as measured by first and third trimester A1c between insulin glargine and NPH insulin [54].

**Detemir:** Detemir is a long-acting insulin analogue that is not as well studied as glargine. The first published report of detemir use in pregnancy was a study of 10 women with T1DM who were treated with detemir for a minimum of 3 months preconception. One patient experienced maternal hypoglycemia, 2 infants were LGA, one experienced neonatal hypoglycemia, and none had congenital malformations. Improved A1c was documented from the beginning of pregnancy ( $8.1 \pm 1.9$ ) to the end ( $5.9 \pm 0.7$ ) (no  $p$ -value reported) [55].

A retrospective case series of 18 women with T1DM and T2DM was published by Shenoy et al. [56] (see [Table 5a & 5b](#)). The authors reported only one event of severe maternal hypoglycemia. Half of the infants were LGA, and 13 of 18 infants experienced neonatal hypoglycemia. Maternal glycemic control improved from preconception (8.6%) to T3 (7.0%) [56].

A large open-label, randomized, parallel-group study of women with T1DM had results published by Mathieson et al. & Hod et al. [57,58] (see [Table 5a & 5b](#)). Patients were randomized to detemir ( $n = 152$ ) or NPH ( $n = 158$ ) up to 12 months preconception or at 8-12 weeks' gestational age and continued until 6 weeks postpartum. Inclusion criteria include A1c  $< 8\%$  at confirmation of pregnancy. Insulin aspart was used as the bolus insulin. The primary endpoint was A1c at 36 weeks' gestation and secondary endpoints included fasting glucose, major and minor hypoglycemia, and adverse events. The mean A1c at 36 weeks' was 6.27% and 6.33% for detemir and NPH groups, respectively (difference  $-0.06$  [95% CI  $-0.21$  to  $0.08$ ]). Mean fasting glucose was significantly lower in detemir group at 24 ( $p = 0.012$ ) and 36

weeks' gestation ( $p=0.017$ ). Major hypoglycemia events were not significantly different (16% in detemir group, 21% in NPH group).

See Glargine section above for results of Callesen et al. [53].

## Discussion

### Lispro

Insulin lispro has an increased affinity for insulin-like growth factor (IGF-1) receptor versus human insulin, which is concerning for potential fetal growth-stimulating effects [59]. Lispro has the potential to pass via the placenta if it forms immune complexes with immunoglobulins. However, Jovanovic et al. [20] have shown no placental transfer via umbilical blood samples following intravenous administration of lispro during labor and similarly, Holcberg et al. [60] conducted an *in vitro* perfusion study that demonstrated no lispro in the umbilical cord [20,58,59].

The data from observational studies and small randomized trials that we have reviewed, suggest that lispro is safe to use in pregnancy. The majority of studies did not report significant differences in birth weight of neonates delivered from women having either PGDM or GDM, when comparing lispro to regular insulin exposure.

The study by Durnwald et al. [29] is the only publication we identified that demonstrated significantly greater birth weight in the lispro group versus regular insulin [29]. Similarly, Lapolla et al. [26] reported significantly higher rate of LGA infants in lispro group (55.1%) versus regular insulin (39.2%) ( $p<0.0267$ ). They also found higher rate of macrosomia in the lispro group (14.5%) compared to regular insulin (11.5%), although the increase was not significant [26]. The two meta-analysis published by Gonzalez et al. [32] and Lv et al. [33] both reported an increased rate of LGA newborns, along with increased birth weight in the latter. The earlier study only included four studies and limited to T1DM, which does not fully provide compelling evidence. The meta-analysis conducted by Lv et al. [33], which included 24 studies with a total of 3724 women, provided stronger data to support the possibility that insulin lispro is associated with increased birth weight and rate of LGA newborns. However, this significance is not apparent with the use of insulin aspart in comparison to regular insulin. Considering larger wealth of studies on insulin lispro in pregnancy compared to aspart, the meta-analysis may not have been sufficiently powered to see the same effect. By contrast, the small randomized trial by Di Cianni et al. [31] reported birth weight to be significantly increased in the regular insulin group [31]. The majority of published data, however, show no difference in birth weight or rates of macrosomia or LGA infants.

There was no apparent correlation between duration of exposure to lispro and size of infants, since the rate of LGA was similar in those who continued lispro throughout pregnancy to those discontinuing during T1 [26]. Lapolla et al. [26] further speculated these findings may be due to short-lived glycemic peaks of lispro, although this data was not recorded in their study.

Garcia-Dominguez et al. [30] demonstrated a significant increase in neonatal hypoglycemia with lispro use, but the authors suggested that this may have been due to concomitant use of an insulin pump [30]. The remaining data we found did not indicate there was any difference in rates of neonatal hypoglycemia

between those exposed to *in utero* to regular insulin versus lispro.

Another concern regarding lispro comes from a case series of 3 women from Kitzmiller et al. [60] who reported the development of diabetic retinopathy [60]. However, Loukovaara et al. [23] demonstrated that lispro had no impact on the progression of diabetic retinopathy [23]. Masson et al. [17] similarly reported that none of the patients developed retinopathy *de novo*, but 6 patients with established retinopathy required laser therapy during pregnancy [17]. Similarly, Buchbinder et al. [21] showed no change in retinopathy status in patients using lispro, but demonstrated change in 6 patients using regular insulin (extensive proliferative retinopathy developed in one patient, mild background retinopathy developed in 3 patients, progression of retinopathy occurred in 2 patients) [21]. Persson et al. [27] showed development of proliferative retinopathy in one patient in regular insulin group and similar development of mild to moderate background retinopathy in both groups [27].

In terms of rates of congenital malformations, none of the studies we reviewed demonstrated a difference between lispro and regular insulin use. Persson et al. [27] reported one congenital malformation with human insulin, but since randomization did not occur until 14 weeks gestation, this finding should not be attributable to treatments used in the study [27]. Also, Aydin et al. [25] demonstrated congenital anomalies in 9 infants born to women who were treated with regular insulin versus none in the lispro group, although differences were not significant [25].

There appears to be a clear advantage of using lispro for its reduction in incidence of maternal hypoglycemia. Garcia-Dominguez et al. [30] were able to demonstrate significantly lower rates of maternal hypoglycemia in lispro group versus regular insulin [30]. Interestingly, Persson et al. [27] showed a significant increase biochemical hypoglycemia ( $<54$  mg/dL) in the lispro group, although no episodes of severe hypoglycemia were demonstrated [27]. The studies observed postprandial glycemia consistently decreased, particularly 1-hour postprandially [12,20,27,31]. Of the studies that measured fasting glycemia, there were no differences between lispro and regular insulin [12,20,27,31].

As suggested by these results glycemic control measured by A1c was improved in lispro groups versus regular insulin in multiple studies [22,23,26,29], except for the Garcia-Dominguez et al. [30] report showing greater A1c levels in the lispro group,  $p=0.022$  [30].

### Aspart

Unlike lispro, aspart exhibits the same affinity for IGF-1 receptor as human insulin [6]. However, only a small body of literature exists on the use of aspart in women with either PGDM or GDM. Of the smaller of the 3 randomized studies, Pettitt et al. [34] found aspart to be superior in terms of glycemic profile over 240 minutes [34]. Another report demonstrated a significant improvement of 1-hour postprandial glucose levels with aspart when compared to regular insulin, suggesting a similar advantage in the control of postprandial glycemia as is provided by lispro [31].

A larger randomized trial reported by Mathiesen et al. [13] and

Hod et al. [14] reported no difference in the incidences of major maternal hypoglycemia and congenital malformations [13,14]. Glycemic control was also comparable between groups. Aspart use resulted in greater overall treatment satisfaction and willingness to continue with the treatment, primarily due to increased flexibility of treatment. Thus, this regimen appears to facilitate treatment compliance. This may be particularly important when considering treating women with insulin, a management decision with the potential to affect disease progression and maternal and neonatal morbidity and mortality.

See the Lispro section above for the results of the meta-analysis by Lv et al. [33].

### Glargine

Similar to lispro, glargine has an increased affinity for IGF-1 receptor compared to human insulin [6]. IGF-1 may have a role in the development of diabetic retinopathy, as well as development of tumors of bone, mammary and ovarian tumors, as supported by in vitro studies on human osteosarcoma cells showing the mitogenic potential of glargine [7]. Hence, the concern for glargine interfering with fetal development [62]. However, studies in rats and mice failed to show an increase in tumor formation with prolonged glargine exposure [49,63]. Furthermore, Pollex et al. [62] carried out an in vitro transplacental transfer study and demonstrated undetectable transfer of glargine at therapeutic concentrations of 150 pmol/L [64].

The studies we have reviewed that investigated glargine use during pregnancy, supports its safety with possible advantages of improved efficacy of achieving fasting and postprandial glycemic targets. In addition, our review found support for glargine-associated reduction in maternal hypoglycemia. Negrato et al. [52] demonstrated that maternal complications tended to occur in women with PGDM; these included progression of retinopathy, nephropathy, preeclampsia, proteinuria and hypoglycemia [52]. A statistically significant improvement of mean A1c change from T1 to T3 was demonstrated by Poyhonen-Alho et al. [48]. All studies reviewed, reported either no difference in the rate of maternal hypoglycemia or a significantly decreased rate compared to NPH [15,46-48,50,52,53].

The data we identified also suggest that there is no difference in neonatal outcomes, including birth weight, neonatal hypoglycemia, and the incidence of congenital malformations. With one exception, there was a significant increase in shoulder dystocia in the glargine group in findings reported by Egerman et al. [51]. The authors speculated the pharmacokinetic profile of glargine may reduce the transfer of metabolic fuel across the trophoblast, although evidence to support this hypothesis is lacking [51].

### Detemir

Detemir has reduced affinity for IGF-1 receptor [59]. Its use in pregnancy has not been widely studied. The only comparative analysis published, compared maternal and neonatal outcomes to glargine [53]. Callesen et al. established comparable glycemic and pregnancy outcomes, except for significantly lower mean birth weight and incidence of LGA infants in the glargine group. This suggests that the peakless glycemic profile of glargine may confer some advantage in pregnancy.

The only randomized trial of over 300 subjects, compared detemir to NPH and found glycemic control and major hypoglycemic events to be comparable at 36 weeks' gestational age. The only statistically significant finding was a lower mean fasting glucose in the detemir group [57,58]. The limited body of data on detemir use during pregnancy thus prohibits us from drawing conclusions.

### Basal-Bolus Therapy with Rapid and Long-Acting Insulin Analogues

Umpierrez et al. [65] have demonstrated the superiority of glycemic control (regarding hyperglycemia and hypoglycemia episodes) with BBT using glargine and glulisine, over sliding-scale insulin therapy with regular insulin, in a randomized trial of 130 adults with T2DM [65]. The comparative studies we reviewed that utilized BBT comprised of rapid- and short-acting analogues with a long-acting analogue, in their treatment regimens during pregnancy, have demonstrated no significant increase in maternal and neonatal risks compared to conventional therapy.

We have identified evidence indicating that the use of rapid- and long-acting insulin analogues is safe in pregnancy. Studies have established these hypoglycemic agents do not cross the placenta [16,59,60,64]. There appears to be clinical advantages of the prenatal use of insulin analogues, such as lispro use being associated with improved levels of postprandial glucose. Timely initiation of insulin treatment to achieve preprandial glucose targets of <90 mg/dL and 2-hour postprandial glucose targets of <120 mg/dL, have been associated with lower risks of fetal and maternal complications [2,4,6,7].

Studies in non-pregnant patients show that BBT compared to NPH plus regular insulin or sliding scale insulin replacement, is superior in terms of achieving glycemic targets and lower risk of severe hypoglycemia [65]. BBT is standard in non-pregnant individuals affected by T1DM or T2DM. Advantages of BBT when compared to conventional insulin therapy include the convenience of flexible pre- and post-dosing of bolus therapy with once daily dosing for basal insulin. Furthermore, the use of insulin analogues allows for stringent glycemic control during pregnancy with minimal glucose excursions throughout the day [6]. Our review provides support for use of BBT with insulin analogues when glycemic targets are not met with the use of nutrition therapy or oral hypoglycemic agents. The use of BBT during pregnancy is not only associated with improved perinatal outcomes, but it will also allow for continuing standard medical treatment from preconception until after the postpartum period. The only opposing evidence proposed by one meta-analysis suggesting that insulin lispro is associated with increased birth weight and LGA rates in newborns, while finding no other differences in any other maternal or neonatal outcome for lispro, aspart, glargine, and detemir in comparison to regular and NPH insulin. While our review found a wealth of evidence to suggest otherwise, it propels us to conclude the demand for rigorous, high-quality, and sufficiently powered randomized clinical trials.

### Conclusion

(1) Insulin analogue use in pregnancy complicated by diabetes has been associated with decreases in A1C, less maternal and neonatal hypoglycemia, when compared to conventional insulins (regular and NPH).

- (2) Although these studies are inadequately powered to definitively conclude an absence of adverse effect associated with insulin analogue therapy in pregnancy, rapid- and long-acting insulin analogue therapy during pregnancy has not been associated with any adverse maternal and neonatal outcome. Further high quality and adequately powered randomized clinical trials need to be conducted to determine true associations of insulin analogues to adverse outcomes.
- (3) Adoption of BBT would facilitate continuity of standard insulin treatment from preconception through the postpartum periods.

### Acknowledgement

Special thanks to Ms. Judith Wilkinson, Medical Librarian, from Lincoln Medical and Mental Health Center Science Library for assistance in findings the reference articles.

### References

- Bolli GB (2004) Type 1 diabetes mellitus: effective insulin strategies with less hypoglycemia. *Postgrad Med* 116(5 Suppl Exploring): 13-20.
- Lambert K, Holt RI (2013) The use of insulin analogues in pregnancy. *Diabetes Obes Metab* 15(10): 888-900.
- Evers IM, de Valk HW, Visser GH (2004) Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 328(7445): 915.
- Damm P, Mersebach H, Råstam J, Kaaja R, Hod M, et al. (2014) Poor pregnancy outcome in women with type 1 diabetes is predicted by elevated HbA1c and spikes of high glucose values in the third trimester. *J Matern Fetal Neonatal Med* 27(2): 149-154.
- McElduff A, Moses RG (2012) Insulin therapy in pregnancy. *Endocrinol Metab Clin North Am* 41(1): 161-173.
- Torlone E, Di Cianni G, Mannino D, Lapolla A (2009) Insulin analogs and pregnancy: an update. *Acta Diabetol* 46(3): 163-172.
- Hirsch IB (2005) Insulin analogues. *N Engl J Med* 352(2): 174-183.
- Mooradian AD, Bernbaum M, Albert SG (2006) Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 145(2): 125-134.
- McCance DR (2011) Pregnancy and diabetes. *Best Pract Res Clin Endocrinol Metab* 25(6): 945-958.
- Rossetti P, Porcellati F, Fanelli CG, Perriello G, Torlone E, et al. (2008) Superiority of insulin analogues versus human insulin in the treatment of diabetes mellitus. *Arch Physiol Biochem* 114(1): 3-10.
- Sharplin P, Gordon J, Peters JR, Tetlow AP, Longman AJ, et al. (2009) Switching from premixed insulin to glargine-based insulin regimen improves glycaemic control in patients with type 1 or type 2 diabetes: a retrospective primary-care-based analysis. *Cardiovasc Diabetol* 8: 9.
- Mecacci F, Carignani L, Cioni R, Bartoli E, Parretti E, et al. (2003) Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. *Eur J Obstet Gynecol Reprod Biol* 111(1): 19-24.
- Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, et al. (2007) Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care* 30(4): 771-776.
- Hod M, Damm P, Kaaja R, Visser GH, Dunne F, et al. (2008) Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 198(2): 186.e1-186.e7.
- Imbergamo MP, Amato MC, Sciortino G, Gambina M, Accidenti M, et al. (2008) Use of glargine in pregnant women with type 1 diabetes mellitus: a case-control study. *Clin Ther* 30(8): 1476-1484.
- Diamond T, Kormas N (1997) Possible adverse fetal effect of insulin lispro. *N Engl J Med* 337(14): 1009.
- Masson EA, Patmore JE, Brash PD, Baxter M, Caldwell G, et al. (2003) Pregnancy outcome in Type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 20(1): 46-50.
- Garg SK, Frias JP, Anil S, Gottlieb PA, MacKenzie T, et al. (2003) Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 9(3): 187-193.
- Wyatt JW, Frias JL, Hoyme HE, Jovanovic L, Kaaja R, et al. (2005) Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med* 22(6): 803-807.
- Jovanovic L, Ilic S, Pettitt DJ, Hugo K, Gutierrez M, et al. (1999) Metabolic and immunologic effects of insulin lispro in gestational diabetes. *Diabetes Care* 22(9): 1422-1427.
- Buchbinder A, Miodovnik M, McElvy S, Rosenn B, Kranias G, et al. (2000) Is insulin lispro associated with the development or progression of diabetic retinopathy during pregnancy? *Am J Obstet Gynecol* 183(5): 1162-1165.
- Bhattacharyya A, Brown S, Hughes S, Vice PA (2001) Insulin lispro and regular insulin in pregnancy. *QJM* 94(5): 255-260.
- Loukovaara S, Immonen I, Teramo KA, Kaaja R (2003) Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care* 26(4): 1193-1198.
- Cypryk K, Sobczak M, Pertyńska-Marczewska M, Zawodniak-Szałapska M, Szymczak W, et al. (2004) Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy. *Med Sci Monit* 10(2): Pi29-Pi32.
- Aydin Y, Berker D, Direktör N, Ustün I, Tütüncü YA, et al. (2008) Is insulin lispro safe in pregnant women: Does it cause any adverse outcomes on infants or mothers? *Diabetes Res Clin Pract* 80(3): 444-448.
- Lapolla A, Dalfrà MG, Spezia R, Anichini R, Bonomo M, et al. (2008) Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. *Acta Diabetologica* 45(1): 61-66.
- Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, et al. (2002) Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract* 58(2): 115-121.
- Plank J, Siebenhofer A, Berghold A, Jeitler K, Horvath K, et al. (2005) Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. *Arch Intern Med* 165(12): 1337-1344.
- Durnwald CP, Landon MB (2008) A comparison of lispro and regular insulin for the management of type 1 and type 2 diabetes in pregnancy. *J Matern Fetal Neonatal Med* 21(5): 309-313.
- García-Domínguez M, Herranz L, Hillman N, Martín-Vaquero P, Jáñez M, et al. (2011) Use of insulin lispro during pregnancy in women with pregestational diabetes mellitus. *Med Clin (Barc)* 137(13): 581-586.



31. Di Cianni G, Volpe L, Ghio A, Lencioni C, Cucuru I, et al. (2007) Maternal metabolic control and perinatal outcome in women with gestational diabetes mellitus treated with lispro or aspart insulin: comparison with regular insulin. *Diabetes Care* 30(4): e11.
32. González Blanco C1, Chico Ballesteros A, Gich Saladich I, Corcoy Pla R (2011) Glycemic control and pregnancy outcomes in women with type 1 diabetes mellitus using lispro versus regular insulin: a systematic review and meta-analysis. *Diabetes Technol Ther* 13(9): 907-911.
33. Lv S, Wang J, Xu Y (2015) Safety of insulin analogs during pregnancy: a meta-analysis. *Arch Gynecol Obstet* 292(4): 749-756.
34. Pettitt DJ, Ospina P, Kolaczynski JW, Jovanovic L (2003) Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 26(1): 183-186.
35. Heller S, Damm P, Mersebach H, Skjøth TV, Kaaja R, et al. (2010) Hypoglycemia in type 1 diabetic pregnancy: role of preconception insulin aspart treatment in a randomized study. *Diabetes Care* 33(3): 473-477.
36. Devlin JT, Hothersall L, Wilkis JL (2002) Use of insulin glargine during pregnancy in a type 1 diabetic woman. *Diabetes Care* 25(6): 1095-1096.
37. Di Cianni G, Volpe L, Lencioni C, Chatzianagnostou K, Cucuru I, et al. (2005) Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 28(4): 982-983.
38. Dolci M, Mori M, Baccetti F (2005) Use of glargine insulin before and during pregnancy in a woman with type 1 diabetes and Addison's Disease. *Diabetes Care* 28(8): 2084-2085.
39. Graves DE, White JC, Kirk JK (2006) The use of insulin glargine with gestational diabetes mellitus. *Diabetes Care* 29(2): 471-472.
40. Torlone E, Gennarini A, Ricci NB, Bolli GB (2007) Successful use of insulin glargine during entire pregnancy until delivery in six Type 1 diabetic women. *Eur J Obstet Gynecol Reprod Biol* 132(2): 238-239.
41. Woolderink JM, van Loon AJ, Storms F, de Heide L, Hoogenberg K (2005) Use of insulin glargine during pregnancy in seven type 1 diabetic women. *Diabetes Care* 28(10): 2594-2595.
42. Caronna S, Cioni F, Dall'Aglio E, Arsenio L (2006) Pregnancy and the long-acting insulin analogue: a case study. *Acta Biomed* 77(1): 24-26.
43. Gallen IW, Jaap A, Roland JM, Chirayath HH (2008) Survey of glargine use in 115 pregnant women with Type 1 diabetes. *Diabet Med* 25(2): 165-169.
44. Lepercq J, Jacqueminet S, Hieronimus S, Timsit J, Grimaldi A (2010) Use of insulin glargine throughout pregnancy in 102 women with type 1 diabetes. *Diabetes Metab* 36(3): 209-212.
45. Henderson CE, Machupalli S, Marcano-Vasquez H, Kerr P, Reilly KD (2009) A retrospective review of glargine use in pregnancy. *J Reprod Med* 54(4): 208-210.
46. Di Cianni G, Torlone E, Lencioni C, Bonomo M, Di Benedetto A, et al. (2008) Perinatal outcomes associated with the use of glargine during pregnancy. *Diabet Med* 25(8): 993-996.
47. Price N, Bartlett C, Gillmer M (2007) Use of insulin glargine during pregnancy: a case-control pilot study. *BJOG* 114(4): 453-457.
48. Pöyhönen-Alho M, Rönnemaa T, Saltevo J, Ekblad U, Kaaja RJ (2007) Use of insulin glargine during pregnancy. *Acta Obstet Gynecol Scand* 86(10): 1171-1174.
49. Smith JG, Manuck TA, White J, Merrill DC (2009) Insulin glargine versus neutral protamine Hagedorn insulin for treatment of diabetes in pregnancy. *Am J Perinatol* 26(1): 57-62.
50. Fang YM, MacKeen D, Egan JF, Zelop CM (2009) Insulin glargine compared with Neutral Protamine Hagedorn insulin in the treatment of pregnant diabetics. *J Matern Fetal Neonatal Med* 22(3): 249-253.
51. Egerman RS, Ramsey RD, Kao LW, Bringman JJ, Haerian H, et al. (2009) Perinatal outcomes in pregnancies managed with antenatal insulin glargine. *Am J Perinatol* 26(8): 591-595.
52. Negrato CA, Rafacho A, Negrato G, Teixeira MF, Araújo CA, et al. (2010) Glargine vs. NPH insulin therapy in pregnancies complicated by diabetes: an observational cohort study. *Diabetes Res Clin Pract* 89(1): 46-51.
53. Callesen NF, Damm J, Mathiesen JM, Ringholm L, Damm P, et al. (2013) Treatment with the long-acting insulin analogues detemir or glargine during pregnancy in women with type 1 diabetes: comparison of glycaemic control and pregnancy outcome. *J Matern Fetal Neonatal Med* 26(6): 588-592.
54. Lepercq J, Lin J, Hall GC, Wang E, Dain MP, et al. (2012) Meta-Analysis of Maternal and Neonatal Outcomes Associated with the Use of Insulin Glargine versus NPH Insulin during Pregnancy. *Obstet Gynecol Int* 2012: 649070.
55. Lapolla A, Di Cianni G, Bruttomesso D, Dalfrà MG, Fresa R, et al. (2009) Use of insulin detemir in pregnancy: a report on 10 Type 1 diabetic women. *Diabet Med* 26(11): 1181-1182.
56. Shenoy VV, Cook SJ, Parry AF, McIntyre HD (2012) Audit of insulin detemir in pregnancy: a retrospective case series. *Diabet Med* 29(7): 958-959.
57. Mathiesen ER, Hod M, Ivanisevic M, Duran Garcia S, Brøndsted L, et al. (2012) Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care* 35(10): 2012-2017.
58. Hod M, Mathiesen ER, Jovanović L, McCance DR, Ivanisevic M, et al. (2014) A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med* 27(1): 7-13.
59. Durnwald CP (2013) Insulin analogues in the treatment of gestational diabetes mellitus. *Clin Obstet Gynecol* 56(4): 816-826.
60. Holcberg G, Tsadkin-Tamir M, Sapir O, Wiznizer A, Segal D, et al. (2004) Transfer of insulin lispro across the human placenta. *Eur J Obstet Gynecol Reprod Biol* 115(1): 117-118.
61. Kitzmiller JL, Main E, Ward B, Theiss T, Peterson DL (1999) Insulin lispro and the development of proliferative diabetic retinopathy during pregnancy. *Diabetes Care* 22(5): 874-876.
62. Pollex E, Moretti ME, Koren G, Feig DS (2011) Safety of insulin glargine use in pregnancy: a systematic review and meta-analysis. *Ann Pharmacother* 45(1): 9-16.
63. Stammlerberger I, Bube A, Durchfeld-Meyer B, Donaubaauer H, Troschau G (2002) Evaluation of the carcinogenic potential of insulin glargine (LANTUS) in rats and mice. *Int J Toxicol* 21(3): 171-179.
64. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G (2010) Insulin glargine safety in pregnancy: a transplacental transfer study. *Diabetes Care* 33(1): 29-33.
65. Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, et al. (2007) Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 30(9): 2181-2186.